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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,591	08/27/2003	Noubar B. Afeyan	COTH-P02-001	7918

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ROPES & GRAY LLP  
IPRM - Floor 43  
Prudential Tower  
800 Boylston Street  
Boston, MA 02199-3600

EXAMINER
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MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
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1652

NOTIFICATION DATE	DELIVERY MODE
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ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

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<b>Office Action Summary</b>	<b>Application No.</b> 10/650,591	<b>Applicant(s)</b> AFEYAN ET AL.
	<b>Examiner</b> MD. YOUNUS MEAH	<b>Art Unit</b> 1652

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 26 May 2011.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,4,5,19,21-34,37-40 and 43 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 4-5, 19, 21-34, 37-40 and 43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |  |
|--|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)<br>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)<br>3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/26/11</u> . | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____.<br>5) <input type="checkbox"/> Notice of Informal Patent Application<br>6) <input type="checkbox"/> Other: _____. |
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### **DETAILED ACTION**

Claims 1, 4-5, 19, 21-34, 37-40 and 43 are pending. With supplemental amendment, filed 5/26/011, in response the final action, mailed on 1/20/2011, the applicants amended claim 1 and canceled claims 3 and 42.

Applicants' amendment of 5/26/011 is considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

#### ***Claim Rejection - 35 U.S.C 103a***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of Claims 1, 3-4, 21-27, 30-34 and 37 under 35 U.S.C. 103(a) by Davis et al (WO00/64485) in view of Chamow et al (Trend Biotech, 1996, 14, pp52-60) and Sallberg et al. (US 6960569) as discussed in the prior office action is withdrawn after amendment of claim 1. However Davis et al (WO00/64485) and Chamow et al (Trend Biotech, 1996, 14, pp52-60) are used in a new rejection as described below:

Claims 1, 3-5, 21--34, 37 43 are rejected under 35 U.S.C. 103(a) by Davis et al (WO00/64485) in view of Chamow et al (Trend Biotech, 1996, 14, pp52-60).

The limitation "protease domain comprises a zymogen when activated" is not given patentability weight because activated zymogen is a protease. Even if patentability weight were to be given, it is obvious because, Davis et al teach fusion

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proteins wherein enzymes (serine protease, (teach applicants' claims 1 and 4), chymotrypsin, matrix metalloprotease, etc) which catalyze degradation of a target are conjugated to targeting (bind to the target) domains, such as a ligand or antibody (page 23, lines 15-30, page 8 lines 20-25, page 15 lines 9-52, wherein protease is conjugated to immunoglobulin, Fab or F(ab)<sub>2</sub>). Davis et al teach that resulting chimeric protein has greater (catalytic, page 8) activity than the unconjugated molecule. The chimeric protein of Davis et al. binds to the target and antagonize/inhibit /degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc (page 28) and degrade component of soil ( page 5, inherently comprises insoluble protein complex). Davis et al teach the said chimeric protein catalyzes the degradation of a target wherein said target comprise blood stains (i.e, insoluble protein-containing aggregate or complex (teach applicant claim 43) , milk stain, etc (Paragraph 0067). Davis et al. use the fusion protein as a pharmaceutical composition (pages 51-56).

However Davis et al do not teach a fusion complex comprising a protease conjugated to constant portion of immunoglobulin heavy chain and second fusion protein comprising a targeting domain conjugated to constant portion of an immunoglobulin heavy chain.

Chamow et al teach bispecific immunoadhesins (immunoglobulin fusion protein) comprising two different proteins having different functions each conjugated to each pair of constant regions of immunoglobulins (table 1 and Fig 3, P-selectin-IgG and E-selectin-IgG ). It is well known in the art the advantages of using the immunoglobulin constant region to make fusion proteins (see, Chamow et al, Trend Biotech, 1996, 14,

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pp52-60, and Ashkenazi et al, Current Opin. of Immunol. 1997, 9, pp 195-200): such as that joining the fusion partner to immunoglobulin facilitates proper folding of domains and function (page 52 right column 2<sup>nd</sup> parag. Chamow et al) by providing antibody type structural properties (by bring them closer, Ashkenazi et al, page 196 left column 2<sup>nd</sup> parag) and increased size often extend in vivo half-life (Ashkenazi et al, page 196 left column 2<sup>nd</sup> parag.). Therefore, one of skill in the art would have been **motivated** to make the fusion complex comprising a stable protease conjugated to constant portion of immunoglobulin heavy chain and a targeting domain conjugated to constant portion of an immunoglobulin heavy chain so that said catalytic domain and targeting domain fusion complex comprise proper folding (via immunoglobulin dimeric binding partner ) so that their effective concentration and function is optimized at the target site.

As such it would have been obvious to one of ordinary skill in the art to use a protease to make a fusion protein (adzyme) as taught by Davis et al and Chamow et al, wherein the protease is conjugated to the constant region of an immunoglobulin heavy chain and a targeting domain comprising an antibody light chain is conjugated to the constant portion of another immunoglobulin heavy chain and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide. One of ordinary skill in the art at the time of the invention was made would have had a reasonable expectation for success for making an adzyme comprising a fusion complex comprising the protease conjugated to constant portion of immunoglobulin heavy chain and a targeting domain conjugated to constant portion of an immunoglobulin heavy chain, because the DNA encoding a protease is known, and

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the molecular biology techniques required to make a recombinant fusion proteins are well known in the art ( Ashkenazi et al, Current Opin. of Immunol. 1997, 9, pp 195-20). Claims 4, 21-22, and 30-34 are included in rejection because of the reason explained below: Claim 4 requires the protease domain to be a specific protease such as a metalloprotease, which is taught by Davis et al. With regard to claims 21-22, Davis et al teach that the substrate can be receptors, signaling molecules like cytokines, EGF-like factors, etc., which are compounds found in a biological fluid of an animal, including blood. Those compounds are endogenous to a human patient (claim 30). With regard to claims 31-32, Davis teaches cytokines as substrates that can be targeted by the adzyme, and since the specification teaches that a substrate that is not significantly affected by the presence of serum albumin is a cytokine, as evidenced by claim 23 of the instant application, Davis teaches that limitation. With regard to claims 33-34, since the adzyme of Davis and Chamow would degrade cytokines, it follows that the half life of the cytokine would be reduced as it would be degraded. Furthermore, by degrading the cytokine, it would necessarily disrupt the interaction between the cytokine and a receptor.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of Chamow et al (Trend Biotech, 1996, 14, pp52-60 as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Dolinar et al. (*Food tecnol and biotech.* 2000, 38, 5-9).

Davis et al., and Chamow et al are described above. However neither Davis et al. nor Chamow et al. teach purification of a fusion protein comprising a protease domain using a reversible protease inhibitor.

Use of protease inhibitor in protein purification is well known in prior art. Dolinar et al. teach MMTS (methyl methane-thiosulfonate), a reversible protease inhibitor in the purification and refolding of a cystine proteinase type protein (page 6, column 2 last parg.). Therefore, one of skill in the art would have been **motivated to** purify **a** fusion protein complex comprising a protease using a protease inhibitor so that said fusion protein complex would not be cleaved by the protease.

As such it would have been obvious to one of ordinary skill in the art to use a protease inhibitor to purify the protease-containing fusion protein complex of Davis et al. and Chamow et al. described above. One of ordinary skill in the art has a reasonable expectation of success at is obtaining an adzyme in view of the teachings of Dolinar et al. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Claims 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of Chamow et al (Trend Biotech, 1996, 14, pp52-60) as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Sanderson et al. (Medic. Res Rev 1999, 19, 179-197:

Davis et al., and Chamow et al. are described above. However, neither Davis et al. nor Chamow et al. teach a pharmaceutical preparation comprising a reversible inhibitor safe to humans.

Sanderson *et al.* (Medic. Res Rev 1999, 19, 179-197) teach a small molecule non-covalent binding protease inhibitor used in a pharmaceutical composition which is reversible and safe to humans (abstract).

Use of protease inhibitors in protein samples is well known in prior art because proteases catalyze the degradation of protein molecules (abstract, page 1, Sanderson et al.). Therefore, in order to inhibit the protease degradation of a pharmaceutical preparation comprising the adzyme of Davis et al. and Chamow et al., one of skill in the art would have been **motivated** to add a reversible protease inhibitor that is safe to humans as taught by Sanderson *et al.* to extend the shelf life of the adzyme.

As such it would have been obvious to one of ordinary skill in the art to make a pharmaceutical preparation comprising the adzyme of Davis et al. and Chamow et al. and combine it with a reversible protease inhibitor as taught by Sanderson et al. so that said pharmaceutical preparation is safe to humans and remains effective. One of ordinary skill in the art has a reasonable expectation of success at making such pharmaceutical composition in view of the fact that protease inhibitors which are safe for humans are known and used in the art as evidenced by Sanderson et al. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

### ***Argument***

Applicants' arguments filed on 05/26/011 have been fully considered, but they found unpersuasive. Applicants argue that their invention is not disclosed nor suggested by the cited prior arts and that the skilled person would have little expectation of success in combining the cited references to derive their invention. Applicants argue that Davis et al do not teach fusion proteins comprising zymogen which when activated becomes as a protease domain. Applicants' arguments have been fully considered, but they found unpersuasive. One of skill in the art know that zymogen when activated turn into a protease. Davis et al teach a fusion protein comprising a protease and the constant portion of an immunoglobulin heavy chain or Chamow et al teach a fusion protein comprising a protease domain and an immunoglobulin heavy chain, these references would anticipate applicants' invention. As explain above, it is obvious to make a fusion protein (adzyme) as taught by Davis et al and Chamow et al, wherein a protease is conjugated to the constant region of an immunoglobulin heavy chain and a targeting domain comprising an antibody light chain is conjugated to the constant portion of another immunoglobulin heavy chain and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Applicants argument for the rejection of claim 5 regarding the use of Dolinar et al in combination of Davis et al. and Chamow et al. is fully considered, but it is found unpersuasive. Dolinar et al teach protease inhibitor in the purification process of

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proteins, therefore it would have been obvious to use protease inhibitor to purify fusion protein of Davis et al. or Chamow et al. as described above.

Applicants argument for the rejection of claims 38-40 regarding the use of Sanderson *et al.* in combination of Davis et al., and Chamow et al. is fully considered, but it is found unpersuasive. Sanderson *et al.* teach a small molecule non-covalent binding protease inhibitor used in a pharmaceutical composition which is reversible and safe to humans (abstract). Use of protease inhibitors in protein samples is well known in prior art because proteases catalyze the degradation of protein molecules (abstract, page 1, Sanderson et al.). Therefore, in order to inhibit the protease degradation of a pharmaceutical preparation comprising the adzyme of Davis et al. and Chamow et al., one of skill in the art would have been **motivated** to add a reversible protease inhibitor that is safe to humans as taught by Sanderson *et al.* to extend the shelf life of the adzyme. Regarding applicants' argument against the rejection of 4, 21-22 and 30-34, applicants' argument has been considered and the reasons why the limitations recited in these claims are obvious over the cited references are explained in the 103(a) rejection above.

### ***Double Patenting Rejection***

The provisional rejection of claims 1, 4-5, 19, 21-34, 37-40 and 43 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-5, 19-27, 30-34, 37-40 of copending Application No.10/792498 is maintained.

Examiner agrees with applicant that the provisional double patenting rejections may be withdrawn when all claims are otherwise allowable if the copending application is not allowable. All the examined claims of the instant application are rejectable on other grounds. Since applicant did not submit terminal disclaimer, the rejections are be maintained.

***Allowable Subject Matter/Conclusion***

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.  
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah  
Patent Examiner, Art Unit 1652

/Tekchand Saidha/  
Primary Examiner, Art Unit 1652